

# ISPOR Forum: COMPARISONS OF FDA AND EMA RISK MANAGEMENT REQUIREMENTS FOR RECENTLY APPROVED PRODUCTS

Dennis W. Raisch, PhD  
Yvonne Lis, PhD

Risk Benefit Management Special Interest Group

## Contributors to Risk Benefit Management Special Interest Group

Contributors	Affiliation
Lis, Yvonne	PAREXEL International
Guo, Jeff J	University of Cincinnati
Lockett, Anthony E	Information Change Limited
Roberts, Melissa	Lovelace Respiratory Research Institute and University of New Mexico
Kamble, Shital	Duke Clinical Research Institute
Raisch, Dennis W	University of New Mexico

### Overview of Forum

- ▶ Background
- ▶ Comparison of FDA and EMA Risk Management approach
- ▶ Analysis of reviewed products
- ▶ Summary and Discussion

### Introduction

Last few years have not been good for risk management  
With failure having at least in part contributed to

- ▶ Banking crisis  
Failure of financial risk management
- ▶ Oil Spill in the Gulf of Mexico  
Failure to manage development and environmental risk
- ▶ Withdrawal of Toyota cars  
Inappropriate use of risk management in manufacturing

## Risk management by the FDA and EMA

- Focussed on risk potential
- Evidence based
- Both act to minimise risk
- Both collect risk data

But how does implementation compare?

## Evolution of Risk Evaluation and Mitigation Strategies (REMs) in the USA

- A system initiated by the FDA under the authority of Food and Drug Administration Drug Administration Amendments Act (FDAAA) of 2007
- Incorporate principles articulated in previous RiskMAP guidance which is mandatory
- Expand monitoring and authority from pre-approval stage to include post approval
- Intent is to assure that benefits of new drugs outweigh their risks
- Provides authority to alter approval status or conditions in the post-marketing period

## When might a REMs be required?

Considerations published by the FDA include;

- Estimated size of population
- Seriousness of disease or condition
- Expected benefit from the drug in comparison with risk
- Expected duration of treatment
- Seriousness of known and /or potential ADR
- Whether a new chemical entity

## Possible components of REMs

- Medication guide
- Patient package insert
- Communication plan
- Elements to assure safe use (ETASU)
- Implementation system if ETASU included
- Timetable for assessment

## Elements to assure safe use (ETASU) – examples

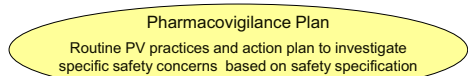
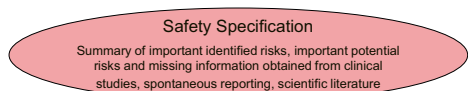
- Healthcare providers who prescribe require training or have experience of use
- Pharmacies, practitioners, or healthcare settings that dispense are specially certified
- The product can only be dispensed in
  - Certain healthcare settings
  - Where there is evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

## Origin of Risk Management Plans (RMPs) in EU

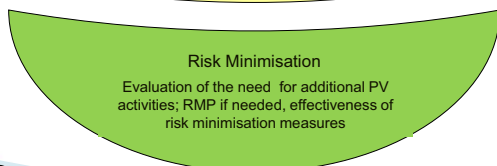
- Agreement reached in 2002 with heads of EU regulatory agencies on need to establish effective pharmacovigilance for medicines or veterinary use products
- EU guidance issued in 2008 – VOLUME 9A of The Rules Governing Medicinal Products in the European Union
  - CHMP Guideline on Risk Management
  - EU Risk Management template (EU-RMP)
- Guidance provided on when to initiate processes and areas where activities are expected

## Components of an EMA Risk Management Plan

### Risk Assessment - Part I



### Risk Minimisation - Part II



## When is a Risk Minimisation Plan required?

- Product contains new active substance
- A significant change in indication
- Products new to a class for which a serious or potentially serious safety risk has been previously identified
- Request by the regulator where a safety risk has been identified and this is perceived to potentially outweigh benefit

## Methods – selection of products (1)

- Identification of New Chemical Entities or Biologicals with both an approved REMS and an European Public Assessment report (EPAR)
- FDA REMs approval dates commencing June 2008
- Public sources used:
  - FDA: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>
  - EMA: <http://www.ema.europa.eu/hmts/human/epar/a.htm>
- Detailed review of REMs and EPARs and any updates posted by Sept 2010

Selection identified 18 NCEs and 11 Biologics

## Methods – selection of products (2)

FDA REMS Components	Total <sup>+</sup>	Not on EMA	On EMA
Medication Guide only	69	50	19
Medication Guide and Communication Plan	18	9	9
Medication Guide, Elements To Assure Safe Use, Implementation System	3	2	1
Medication Guide, Communication Plan, Elements To Assure Safe Use, Implementation System	3	2	1
Communication Plan, Elements To Assure Safe Use, Implementation System	2	2	0
<b>Grand Total</b>	<b>95</b>	<b>65</b>	<b>30*</b>

+ Number retrieved from FDA website on 27<sup>th</sup> Feb 2010  
\* Infergen removed as marketing authorisation withdrawn.

## Comparison of approaches – Antiplatelet NCE

### FDA REMs – March 2010

#### Medication guide

Distributed to every outpatient / inpatient  
Instructions on dispensing for pharmacists

#### Communication plan

Dear healthcare provider letter and prescriber brochure for specialists and primary care physicians to convey information on serious risk of bleeding, appropriate patient selection

Information in healthcare provider brochure to discuss with patients  
Limited to 2 years post launch

#### Elements to assure safe use

None

### EMA RMP – February 2009

#### Safety Specification

**Identified Risks** – Haemorrhage, Anaemia,  
**Potential risks** – off label use, phototoxicity, hepatic injury, allergic reactions, thrombocytopenia, neutropenia, Thrombotic thrombocytopenic purpura

**Missing information** – concomitant use with fibrinolytics, clopidogrel & NSAIDs; pediatric population, pregnant/ lactating women; subjects without clinical manifestations of ACS; subjects with severely compromised cardiac status; subjects with severe hepatic impairment

#### Pharmacovigilance activities

**Identified and potential risks** – Routine and targeted surveillance; Prospective in-hospital Registry for risk of haemorrhage and off label use

**Missing information** – Routine surveillance and additional analysis of AE from clinical trials and safety database

#### Risk Minimisation activities

Contraindications and special warnings in SPC  
Educational materials for treating physicians

## Comparison of approaches – recombinant anti-TNF

### FDA REMs – March 2009

#### Medication guide

Distributed to every patient  
Health care providers

#### Communication plan

Dear healthcare provider letter, web based materials and a medical scientific liaison slide deck

To convey information on the risk of invasive fungal infections, information on signs and symptoms as well as treatment of fungal infection; benefit/risk assessment prior to restarting therapy after recovery from fungal infection

Information in healthcare provider brochure to discuss with patients  
Limited time frame

#### Elements to assure safe use

None

### EMA RMP – October 2009

#### Safety Specification

**Identified Risks** – Infections incl serious opportunistic

**Potential risks** – Malignancies incl lymphoma; congestive heart failure and ischaemic cardiac events; demyelinating like disorders; aplastic anemia; pancytopenia, neutropenia, leukopenia thrombocytopenia; serious bleeding events; lupus and lupus like illness; immunogenicity; hepatitis B reactivation

**Missing information** – Pregnancy and lactation; children, adolescents, elderly; patients with renal or hepatic impairment; immune function; potential for overdose or medication errors; off label use; concomitant use with DMARDs other than MTX; previous use of anti TNF therapy

#### Pharmacovigilance activities

**Identified and potential risks** – Routine and active surveillance using a Registry; evaluation of risk from information gathered in PSURs

**Missing information** – Routine and active surveillance using a Registry; evaluation of risk from information gathered in PSURs

#### Risk Minimisation activities

Contraindications and special warnings in SPC  
Educational programme (target audience not specified in EPAR)

## Overview of Forum

- ▶ Introduction
- ▶ Comparison of FDA and EMA Risk Management approach
- ▶ Analysis of reviewed products
- ▶ Summary and Discussion

## Products Reviewed

### New Chemical Entities (n=18)

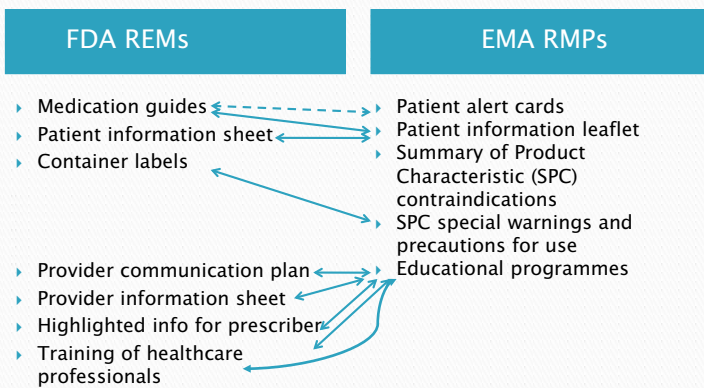
1. Actos (pioglitazone hydrochloride) Tablets
2. Avandamet (rosiglitazone maleate and metformin hydrochloride) Tablets
3. Byetta (exanatide) Injection
4. Effient (prasugrel) Tablets
5. Forteo (teriparatide [rDNA origin]) Injection
6. Kaletra (lopinavir and ritonavir) Oral Solution
7. Keppra, Keppra XR (levetiracetam) Tablets, Extended-Release Tablets, Oral Solution, and Injection
8. Lyrica (pregabalin) Capsules
9. Multaq (dronedarone) Tablets
10. Rebetal (ribavirin) Capsules
11. Samsca (tolvaptan) Tablets
12. Tracleer (bosentan) Tablets
13. Trizivir (abacavir sulfate, lamivudine, and zidovudine)

14. Vimpat (lacosamide) Injection
15. Viramune (nevirapine) Tablets and Oral Suspension
16. Ziagen (abacavir sulfate) Tablets and Oral Solution
17. Zonegran (zonisamide) Capsules
18. Zyprexa, Zyprexa Zydis (olanzapine) Tablets

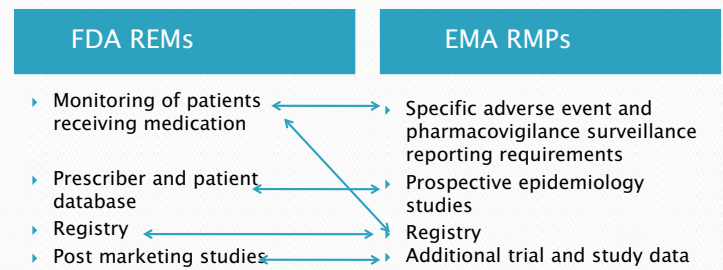
### Biological Products (n=11)

19. Cimzia (certolizumab pegol) Lyophilized powder for solution for subcutaneous injection
20. Enbrel (etanercept) for Subcutaneous Injection
21. Extavia (interferon beta-1b)
22. Intron A (interferon alfa-2a)
23. Nplate (romiplostim) for Subcutaneous Injection
24. Pegasys (peginterferon alfa-2a)
25. PegIntron (peginterferon alfa-2b)
26. Remicade (infliximab) Vial
27. Simponi (golimumab) Injection
28. Stelara (ustekinumab) Injection
29. Xolair (omalizumab) Injection

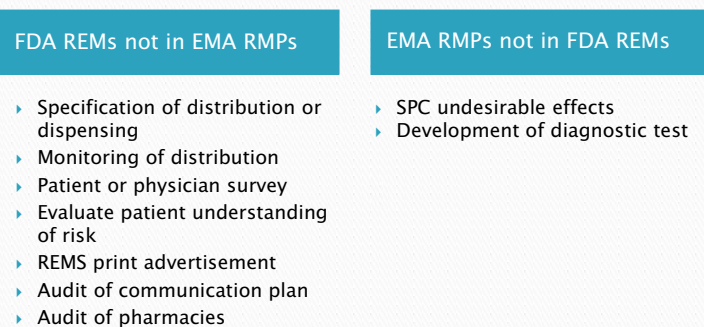
## Key Components Comparison (1)



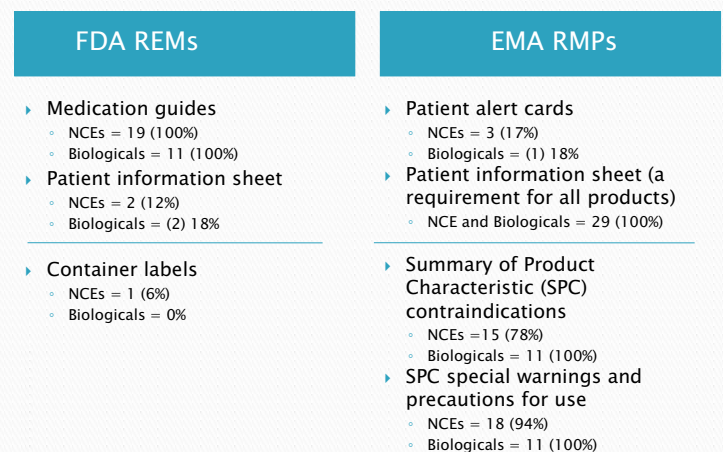
## Key Components Comparison (2)



## Components in sample not evident in both REMs and RMPs



## By product comparison summaries (1)



## By product comparison summaries (2)

FDA REMs	EMA RMPs
<ul style="list-style-type: none"> <li>▶ Provider communication plan                             <ul style="list-style-type: none"> <li>◦ NCEs = 6 (33%)</li> <li>◦ Biologicals = 9 (82%)</li> </ul> </li> <li>▶ Provider information sheet                             <ul style="list-style-type: none"> <li>◦ NCEs = 2 (11%)</li> <li>◦ Biologicals = 2 (18%)</li> </ul> </li> <li>▶ Highlighted info for prescriber                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 0</li> </ul> </li> <li>▶ Training of healthcare professionals                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 0%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▶ Educational programmes                             <ul style="list-style-type: none"> <li>◦ NCEs = 4 (22%)</li> <li>◦ Biologicals = 4 (36%)</li> </ul> </li> </ul>

## By product comparison summaries (3)

FDA REMs	EMA RMPs
<ul style="list-style-type: none"> <li>▶ Monitoring of patients receiving medication                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 1 (9%)</li> </ul> </li> <li>▶ Prescriber and patient database                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 0</li> </ul> </li> <li>▶ Patient Registry                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 3 (27%)</li> </ul> </li> <li>▶ Post marketing studies                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 1 (9%)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▶ Specific adverse event and pharmacovigilance surveillance reporting requirements                             <ul style="list-style-type: none"> <li>◦ NCEs = 12 (61%)</li> <li>◦ Biologicals = 4 (36%)</li> </ul> </li> <li>▶ Prospective epidemiology studies                             <ul style="list-style-type: none"> <li>◦ NCEs = 4 (11%)</li> <li>◦ Biologicals = 5 (45%)</li> </ul> </li> <li>▶ Prospective patient registry                             <ul style="list-style-type: none"> <li>◦ NCEs = 3 (17%)</li> <li>◦ Biologicals = 7 (64%)</li> </ul> </li> <li>▶ Additional trial and study data                             <ul style="list-style-type: none"> <li>◦ NCEs = 19 (100%)</li> <li>◦ Biologicals = 11 (100%)</li> </ul> </li> </ul>

## FDA REMs components not evident in EMA RMPs (1)

<ul style="list-style-type: none"> <li>▶ Specification of distribution or dispensing                             <ul style="list-style-type: none"> <li>◦ NCEs = 11 (56%)</li> <li>◦ Biologicals = 7 (64%)</li> </ul> </li> <li>▶ Monitoring of distribution                             <ul style="list-style-type: none"> <li>◦ NCEs = 0</li> <li>◦ Biologicals = 4 (36%)</li> </ul> </li> <li>▶ Patient or physician survey                             <ul style="list-style-type: none"> <li>◦ NCEs = 3 (17%)</li> <li>◦ Biologicals = 4 (36%)</li> </ul> </li> <li>▶ Review of promotional materials                             <ul style="list-style-type: none"> <li>◦ NCEs = 2 (11%)</li> <li>◦ Biologicals = 0</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▶ Evaluate patient understanding of risk                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 1 (9%)</li> </ul> </li> <li>▶ REMS print advertisement                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 0</li> </ul> </li> <li>▶ Audit of communication plan                             <ul style="list-style-type: none"> <li>◦ NCEs = 0</li> <li>◦ Biologicals = 0</li> </ul> </li> <li>▶ Audit of pharmacies                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 0</li> </ul> </li> </ul>
--	--

## FDA REMs components not evident in EMA RMPs (2)

<ul style="list-style-type: none"> <li>▶ Summary of Product Characteristic Undesirable Effects                             <ul style="list-style-type: none"> <li>◦ NCEs = 13 (72%)</li> <li>◦ Biologicals = 11 (100%)</li> </ul> </li> <li>▶ Development of diagnostic test                             <ul style="list-style-type: none"> <li>◦ NCEs = 1 (6%)</li> <li>◦ Biologicals = 0%</li> </ul> </li> </ul>
--

## Key differences

- ▶ Extensive use of Medication Guides in FDA REMS to communicate risk to patients
- ▶ FDA Communication plan important in communicating risk to healthcare professionals
- ▶ EMA focus on SPC to communicate risk to healthcare professionals
- ▶ Additional Focus of FDA REMS is Evaluation of Impact/Effectiveness of REMS implementation

## Questions

- ▶ What has been the industry experience of developing both an REM and RMP for the same product?
- ▶ From a pharmaceutical company perspective Risk Management plans are expensive, are they really a cost effective way of protecting patients, or a barrier to entry for pharmaceuticals?
- ▶ Do risk management plans actually alter physician behaviour?
- ▶ Has the introduction of REMs and RMPs fundamentally changed the way the industry should naturally want to manage risk?

## Spare question?

- Will risk management programs act as a barrier to research on new indications for old drugs?

